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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|-----------------|-------------|----------------------|---------------------|
|-----------------|-------------|----------------------|---------------------|

09/477,962 01/05/00 SHEN

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HM22/0810

EXAMINER

KERR, K
ART UNIT PAPER NUMBER

1652

DATE MAILED:

08/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/477,962 | SHEN ET AL. | |
| | Examiner | Art Unit | |
| | Kathleen M Kerr | 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 07 July 2001.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-73 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) _____ is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) 1-73 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) Other: _____

DETAILED ACTION

Application Status

1. A response to the Notice to Comply with the Sequence Rules was filed on June 26, 2001; said response (the sequence listing in computer readable form and paper copy) has been entered. A preliminary amendment was also filed on June 26, 2001 to amend Claims 4 and 28 to be in compliance with the sequence rules. Claims 1-73 are pending in the instant application.

Restriction

2. Restriction to one of the following inventions (Groups) is required under 35 U.S.C. 121. Due to the complex nature of the Markush groupings, the Examiner will first separate the subject matter into SuperGroups, then each SuperGroup into Groups for clarity and ease of demonstrating distinctness.

SuperGroup A. Claims 1-21, 23, 40-45, 65-66, 68-69, and 71-73, drawn to nucleic acid sequence encoding any one of open reading frames (ORFs) 8-41, expression vectors thereof, and host cells thereof, classified in class 435, subclass 252.3.

1. Claims of SuperGroup A, relating to ORF 8.
2. Claims of SuperGroup A, relating to ORF 9.
3. Claims of SuperGroup A, relating to ORF 10.
4. Claims of SuperGroup A, relating to ORF 11.
5. Claims of SuperGroup A, relating to ORF 12.
6. Claims of SuperGroup A, relating to ORF 13.
7. Claims of SuperGroup A, relating to ORF 14.

8. Claims of SuperGroup A, relating to ORF 15.
9. Claims of SuperGroup A, relating to ORF 16.
10. Claims of SuperGroup A, relating to ORF 17.
11. Claims of SuperGroup A, relating to ORF 18.
12. Claims of SuperGroup A, relating to ORF 19.
13. Claims of SuperGroup A, relating to ORF 20.
14. Claims of SuperGroup A, relating to ORF 21.
15. Claims of SuperGroup A, relating to ORF 22.
16. Claims of SuperGroup A, relating to ORF 23.
17. Claims of SuperGroup A, relating to ORF 24.
18. Claims of SuperGroup A, relating to ORF 25.
19. Claims of SuperGroup A, relating to ORF 26.
20. Claims of SuperGroup A, relating to ORF 27.
21. Claims of SuperGroup A, relating to ORF 28.
22. Claims of SuperGroup A, relating to ORF 29.
23. Claims of SuperGroup A, relating to ORF 30.
24. Claims of SuperGroup A, relating to ORF 31.
25. Claims of SuperGroup A, relating to ORF 32.
26. Claims of SuperGroup A, relating to ORF 33.
27. Claims of SuperGroup A, relating to ORF 34.
28. Claims of SuperGroup A, relating to ORF 35.
29. Claims of SuperGroup A, relating to ORF 36.

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30. Claims of SuperGroup A, relating to ORF 37.
31. Claims of SuperGroup A, relating to ORF 38.
32. Claims of SuperGroup A, relating to ORF 39.
33. Claims of SuperGroup A, relating to ORF 40.
34. Claims of SuperGroup A, relating to ORF 41.

SuperGroup B. Claims 22, 24-39, and 67, drawn to a multi-functional protein complexes and polypeptides, classified in class 435, subclass 183.

35. Claims of SuperGroup B, relating to ORF 8.
36. Claims of SuperGroup B, relating to ORF 9.
37. Claims of SuperGroup B, relating to ORF 10.
38. Claims of SuperGroup B, relating to ORF 11.
39. Claims of SuperGroup B, relating to ORF 12.
40. Claims of SuperGroup B, relating to ORF 13.
41. Claims of SuperGroup B, relating to ORF 14.
42. Claims of SuperGroup B, relating to ORF 15.
43. Claims of SuperGroup B, relating to ORF 16.
44. Claims of SuperGroup B, relating to ORF 17.
45. Claims of SuperGroup B, relating to ORF 18.
46. Claims of SuperGroup B, relating to ORF 19.
47. Claims of SuperGroup B, relating to ORF 20.
48. Claims of SuperGroup B, relating to ORF 21.
49. Claims of SuperGroup B, relating to ORF 22.

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50. Claims of SuperGroup B, relating to ORF 23.
51. Claims of SuperGroup B, relating to ORF 24.
52. Claims of SuperGroup B, relating to ORF 25.
53. Claims of SuperGroup B, relating to ORF 26.
54. Claims of SuperGroup B, relating to ORF 27.
55. Claims of SuperGroup B, relating to ORF 28.
56. Claims of SuperGroup B, relating to ORF 29.
57. Claims of SuperGroup B, relating to ORF 30.
58. Claims of SuperGroup B, relating to ORF 31.
59. Claims of SuperGroup B, relating to ORF 32.
60. Claims of SuperGroup B, relating to ORF 33.
61. Claims of SuperGroup B, relating to ORF 34.
62. Claims of SuperGroup B, relating to ORF 35.
63. Claims of SuperGroup B, relating to ORF 36.
64. Claims of SuperGroup B, relating to ORF 37.
65. Claims of SuperGroup B, relating to ORF 38.
66. Claims of SuperGroup B, relating to ORF 39.
67. Claims of SuperGroup B, relating to ORF 40.
68. Claims of SuperGroup B, relating to ORF 41.

SuperGroup C. Claims 46-63, drawn to methods of chemically modifying a biological molecule, classified in class 435, subclass 15 (see also election of species below).

69. Claims of SuperGroup C, relating to ORF 8.

70. Claims of SuperGroup C, relating to ORF 9.
71. Claims of SuperGroup C, relating to ORF 10.
72. Claims of SuperGroup C, relating to ORF 11.
73. Claims of SuperGroup C, relating to ORF 12.
74. Claims of SuperGroup C, relating to ORF 13.
75. Claims of SuperGroup C, relating to ORF 14.
76. Claims of SuperGroup C, relating to ORF 15.
77. Claims of SuperGroup C, relating to ORF 16.
78. Claims of SuperGroup C, relating to ORF 17.
79. Claims of SuperGroup C, relating to ORF 18.
80. Claims of SuperGroup C, relating to ORF 19.
81. Claims of SuperGroup C, relating to ORF 20.
82. Claims of SuperGroup C, relating to ORF 21.
83. Claims of SuperGroup C, relating to ORF 22.
84. Claims of SuperGroup C, relating to ORF 23.
85. Claims of SuperGroup C, relating to ORF 24.
86. Claims of SuperGroup C, relating to ORF 25.
87. Claims of SuperGroup C, relating to ORF 26.
88. Claims of SuperGroup C, relating to ORF 27.
89. Claims of SuperGroup C, relating to ORF 28.
90. Claims of SuperGroup C, relating to ORF 29.
91. Claims of SuperGroup C, relating to ORF 30.

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92. Claims of SuperGroup C, relating to ORF 31.
93. Claims of SuperGroup C, relating to ORF 32.
94. Claims of SuperGroup C, relating to ORF 33.
95. Claims of SuperGroup C, relating to ORF 34.
96. Claims of SuperGroup C, relating to ORF 35.
97. Claims of SuperGroup C, relating to ORF 36.
98. Claims of SuperGroup C, relating to ORF 37.
99. Claims of SuperGroup C, relating to ORF 38.
100. Claims of SuperGroup C, relating to ORF 39.
101. Claims of SuperGroup C, relating to ORF 40.
102. Claims of SuperGroup C, relating to ORF 41.

SuperGroup D. Claim 64, drawn to methods of producing a bleomycin compound, classified in class 435, subclass 76.

103. Claims of SuperGroup D, relating to ORF 8.
104. Claims of SuperGroup D, relating to ORF 9.
105. Claims of SuperGroup D, relating to ORF 10.
106. Claims of SuperGroup D, relating to ORF 11.
107. Claims of SuperGroup D, relating to ORF 12.
108. Claims of SuperGroup D, relating to ORF 13.
109. Claims of SuperGroup D, relating to ORF 14.
110. Claims of SuperGroup D, relating to ORF 15.
111. Claims of SuperGroup D, relating to ORF 16.

112. Claims of SuperGroup D, relating to ORF 17.
113. Claims of SuperGroup D, relating to ORF 18.
114. Claims of SuperGroup D, relating to ORF 19.
115. Claims of SuperGroup D, relating to ORF 20.
116. Claims of SuperGroup D, relating to ORF 21.
117. Claims of SuperGroup D, relating to ORF 22.
118. Claims of SuperGroup D, relating to ORF 23.
119. Claims of SuperGroup D, relating to ORF 24.
120. Claims of SuperGroup D, relating to ORF 25.
121. Claims of SuperGroup D, relating to ORF 26.
122. Claims of SuperGroup D, relating to ORF 27.
123. Claims of SuperGroup D, relating to ORF 28.
124. Claims of SuperGroup D, relating to ORF 29.
125. Claims of SuperGroup D, relating to ORF 30.
126. Claims of SuperGroup D, relating to ORF 31.
127. Claims of SuperGroup D, relating to ORF 32.
128. Claims of SuperGroup D, relating to ORF 33.
129. Claims of SuperGroup D, relating to ORF 34.
130. Claims of SuperGroup D, relating to ORF 35.
131. Claims of SuperGroup D, relating to ORF 36.
132. Claims of SuperGroup D, relating to ORF 37.
133. Claims of SuperGroup D, relating to ORF 38.

134. Claims of SuperGroup D, relating to ORF 39.
135. Claims of SuperGroup D, relating to ORF 40.
136. Claims of SuperGroup D, relating to ORF 41.

SuperGroup E. Claim 70, drawn to methods of converting an apo-carrier protein to a holo-carrier protein, classified in class 435, subclass 15.

137. Claims of SuperGroup E, relating to ORF 8.
138. Claims of SuperGroup E, relating to ORF 9.
139. Claims of SuperGroup E, relating to ORF 10.
140. Claims of SuperGroup E, relating to ORF 11.
141. Claims of SuperGroup E, relating to ORF 12.
142. Claims of SuperGroup E, relating to ORF 13.
143. Claims of SuperGroup E, relating to ORF 14.
144. Claims of SuperGroup E, relating to ORF 15.
145. Claims of SuperGroup E, relating to ORF 16.
146. Claims of SuperGroup E, relating to ORF 17.
147. Claims of SuperGroup E, relating to ORF 18.
148. Claims of SuperGroup E, relating to ORF 19.
149. Claims of SuperGroup E, relating to ORF 20.
150. Claims of SuperGroup E, relating to ORF 21.
151. Claims of SuperGroup E, relating to ORF 22.
152. Claims of SuperGroup E, relating to ORF 23.
153. Claims of SuperGroup E, relating to ORF 24.

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154. Claims of SuperGroup E, relating to ORF 25.
155. Claims of SuperGroup E, relating to ORF 26.
156. Claims of SuperGroup E, relating to ORF 27.
157. Claims of SuperGroup E, relating to ORF 28.
158. Claims of SuperGroup E, relating to ORF 29.
159. Claims of SuperGroup E, relating to ORF 30.
160. Claims of SuperGroup E, relating to ORF 31.
161. Claims of SuperGroup E, relating to ORF 32.
162. Claims of SuperGroup E, relating to ORF 33.
163. Claims of SuperGroup E, relating to ORF 34.
164. Claims of SuperGroup E, relating to ORF 35.
165. Claims of SuperGroup E, relating to ORF 36.
166. Claims of SuperGroup E, relating to ORF 37.
167. Claims of SuperGroup E, relating to ORF 38.
168. Claims of SuperGroup E, relating to ORF 39.
169. Claims of SuperGroup E, relating to ORF 40.
170. Claims of SuperGroup E, relating to ORF 41.

The Examiner notes that, for SuperGroups C-E, not all ORFs may be pertinent to the general methods. For example, only particular ORFs encode enzymes able to couple a first amino acid to a second amino acid (a species of method in SuperGroup C). Thus, all 34 Groups in any particular SuperGroup C-E *may* not be relevant; 170 Groups is the maximum number of inventions in the instant application.

3. The inventions are distinct, each from the other because of the following reasons:

The Groups within SuperGroup A (Groups 1-34) are related to each other as nucleic acids encoding polyketide synthase enzymes which together can produce bleomycin-like polyketides. However, these nucleic acids encode enzymes which each have distinct functional properties catalyzing unique reactions in the biosynthetic pathway of the polyketide bleomycin. Furthermore, these nucleic acids encode enzymes having distinct structural properties with varying amino acid sequence, and thus varying nucleic acid sequence, lacking any consensus among the Groups. Moreover, each of these nucleic acids encode enzymes, or pieces thereof, which can be used in a distinct process from the biosynthesis of the polyketide bleomycin, such as in (1) domain swapping methods for use in other modular PKSs and/or peptide synthetases or in (2) hybridization techniques to identify related PKS genes in other microorganisms. Thus, members of SuperGroup A (Groups 1-34) are patentably distinct, each from the other.

The Groups within SuperGroup B (Groups 35-68) are related polyketide synthase or peptide synthetase enzymes which together can produce bleomycin-like polyketides. These enzymes are distinct from each other for the reasons cited above for their encoding nucleic acids. Thus, members of SuperGroup B (Groups 35-68) are patentably distinct, each from the other.

The methods of SuperGroup C (Groups 69-102), SuperGroup D (Groups 103-136), and SuperGroup E (Groups 137-170) are related, within their respective SuperGroups, as methods of using distinct nucleic acids encoding bleomycin biosynthetic enzymes, or the distinct enzymes themselves, which together can produce bleomycin-like polyketides. The methods within each SuperGroup are distinct from every other method in the SuperGroup for the reasons cited above for the distinctness of the nucleic acids and/or the enzymes. Thus, members of SuperGroup C

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(Groups 69-102) are patentably distinct, each from the other. Members of SuperGroup D (Groups 103-136) are patentably distinct, each from the other. And members of SuperGroup E (Groups 137-170) are patentably distinct, each from the other.

The nucleic acids of SuperGroup A are each respectively related to the enzymes (of the same ORF) of SuperGroup B by virtue of the fact that the nucleic acids encode the enzymes.

The nucleic acids have utility for the recombinant production of the enzyme in a host cell.

Although the nucleic acids and the enzymes are related, they are distinct inventions because the enzyme product can be made by other and materially distinct processes, such as purification from a natural source. Furthermore, nucleic acids can be used for processes other than the production of enzyme, such as nucleic acid hybridization assays. Therefore, respective members of SuperGroups A and B are patentably distinct.

The nucleic acids of SuperGroups A and B are related the respective (same ORF) methods of SuperGroups C-E as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process-for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the nucleic acids can be used in processes other than the methods of SuperGroups C-E, such as in hybridization assays; and the enzymes can be used in processes other than the methods of SuperGroups C-E, such as in the *in vivo* production of antibodies. Therefore, Groups of SuperGroups A and B are patentably distinct from any of the Groups in SuperGroups C-E.

The respective (same ORF) methods of SuperGroups C-E are related as methods of using the same products, either nucleic acids or encoded enzymes of the bleomycin biosynthetic

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pathway. However, the methods (C-E) are distinct from each other because they utilize distinct methods steps and distinct reagents (except for the related ORF as nucleic acid or enzyme) to produce distinct products. Thus, the respective methods of SuperGroups C-E are patentably distinct, each from the other.

In addition to the distinctness noted above, the Examiner will further expound on the distinctness between open reading frames. Gene clusters are becoming more common in the art, and, therefore, larger sequences are being claimed as continuous sequences. However, SEQ ID NO:1, as disclosed, was not isolated as a continuous sequence, nor does it encode one open reading frame. Moreover, in the art of polyketide synthases, each open reading frame (ORF) or, in some cases each individual domain of every module of every open reading frame, has utility by itself for use in domain swapping among other PKS genes. These domains and modules are often in a combination that is the ORF. While the ORFs are often in combination with other ORFs to form clusters, these ORFs are each independent proteins, with distinct primary, secondary, and tertiary structures, wherein the basis for restriction lies.

In addition to the distinctness between open reading frames, to search any one ORF in a single application is unduly burdensome due to the large sequence; however, without distinctness, such a burden cannot be the basis of restriction. Moreover, the inclusion of more than one ORF, which in and of itself is unduly burdensome to search, would constitute an **enormous** search burden on the Examiner due to the extensive sequence searching required considering not only lengthy sequences, but also all the useful fragments (domains and modules) thereof.

Restriction of Species

4. This application contains claims directed to the following patentably distinct species of the claimed invention of SuperGroup C (Claims 46-63):

- a) Methods of coupling a first amino acid to a second amino acid (Claims 58-61)
- b) Methods of coupling a first fatty acid to a fatty amino acid (Claims 62-63)

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, Claims 46-57 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103(a) of the other invention.

Election of Invention/Species

5. A telephone call was made to Thomas Hunter on August 5, 2001 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. § 1.143).

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(i).

Notice of Possible Rejoinder

7. The Examiner notes some claims in SuperGroups C-E are drawn to methods of using either (1) nucleic acids encoding bleomycin biosynthetic enzymes or (2) bleomycin biosynthetic enzymes themselves. If product claims, that is claims drawn to either the nucleic acids (out of SuperGroup A) or the enzymes (out of SuperGroup B), are found to be allowable, any claims drawn to methods of using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, would now be rejoined pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also M.P.E.P. § 821.04, *In re Ochiai*, and *In re Brouwer*). Since some process Claims 46-63, 64, and 70 would be rejoined

and fully examined for patentability under 37 C.F.R. § 1.104, Applicants are instructed to amend said claims as deemed necessary according to rejections made against the elected claims.

Conclusion

8. In response to the instant Office action, Applicants must **elect** an invention (**Group - not** a SuperGroup) to be examined. If any Group in SuperGroup C is elected, an election of species is also required for examination if the generic claims are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



PONNATHUPURA ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

KMK
August 5, 2001